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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,248	MITCHELL ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34 and 36-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,11,13,14,16-23,25,26,28,29,31-34,36-40,42,43,45,46,48-51,53-60* is/are rejected.

7)☒ Claim(s) *9,12,15-30,41,44,47 and 52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/18/05;5/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This case was transferred to examiner Teresa Strzelecka of Art Unit 1637 due to temporary absence of examiner Cynthia Wilder from the USPTO.

2. This office action is in response to an amendment filed January 30, 2006. Claims 1-34 and 36-60 were previously pending. Applicants did not amend any claims.

3. The rejection of claims 1-30, 36-47 and 50-52 under 35 U.S.C. 112, first paragraph, enablement, is withdrawn.

4. Applicants' submission of a terminal disclaimer obviated the obviousness-type double patenting rejection of claims 1-33, 36-47 and 50-60 over claims 1-27 of U.S. Patent No. 6,083,702; the obviousness-type double patenting rejection of claims 1-34, 36-47 and 50-60 over claims 1-6, 9-18 and 28-32 of U.S. Patent No. 6,280,978; provisional obviousness-type double patenting rejection of claims 1-34, 36-47 and 50-60 over claims 1-51 of the patent application No. 09/756,096; provisional obviousness-type double patenting rejection of claims 1-34, 36-47 and 50-60 over claims 1-23, 28-35 and 37-39 of the patent application No. 09/941,492; provisional obviousness-type double patenting rejection of claims 1-34, 36-47 and 50-60 over claims 1-6, 9-23 and 28-34 of the patent application No. 09/838,858; provisional obviousness-type double patenting rejection of claims 1-34, 36-47 and 50-60 over claims 1-8, 10-21 and 23-39 of the patent application No. 10/456,153.

5. Applicants' arguments are moot in view of new grounds for rejection presented in this office action.

Claim Objections

6. Claim 11 is objected to because of the following informalities: the claim does not end in a period. Appropriate correction is required.

7. Claims 16-30 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 1-15, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 16-30 are identical to claims 1-15, respectively.

8. Applicant is advised that should claims 1-15 be found allowable, claims 16-30 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 54-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing of chimeric RNA molecules in cells in vitro, does not reasonably provide enablement for performing the method in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 54-60 are broadly drawn to methods of creating chimeric RNA molecules in cells by contacting the cells with nucleic acid molecules comprising target binding domain, 3' splice (or 5') region and nucleotide sequence to be trans-spliced to target pre-mRNA. These claims therefore encompass in vivo and in vitro methods. However, as will be further discussed, there is no support in the specification and prior art for the in vivo methods, only for in vitro methods. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification.

The specification provides no evidence that the disclosed trans-splicing constructs, named by Applicants "pre-trans splicing molecules, (PTMs), would be able to achieve generation of chimeric RNA molecules in vivo, for example, in humans or in a living animal or in plants. On pages 28-31 of the specification Applicants discuss targeting of the human β-chronic gonadotropin-6 (β hCG6) and CFTR genes, but no examples were provided which evidence that it can be achieved in vivo. The examples provided on pages 35-40 show correction of the defective LacZ gene in 293T cells in vitro, and, as indicated in Fig. 7, shows that the efficiency of splicing was

dependent on whether the RNA was capped or not, and that splicing was achieved for a non-specific target of CFTR. There is no evidence that trans-splicing can be achieved in vivo with reasonable efficiency and specificity. Therefore, the guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Working Examples

The specification has no working examples of in vivo production of chimeric mRNA molecules using the PTMs and trans-splicing. While there is an in vitro example involving 293T cells and restoration of the LacZ gene activity, the efficiency and specificity of the reactions are low.

The unpredictability of the art and the state of the prior art

On pages 28-31 of the specification Applicants discuss targeting of the human β-chronic gonadotropin-6 (β hCG6) and CFTR genes, but no examples were provided which evidence that it can be achieved in vivo. The examples provided on pages 35-40 show correction of the defective LacZ gene in 293T cells in vitro, and, as indicated in Fig. 7, shows that the efficiency of splicing was dependent on whether the RNA was capped or not, and that splicing was achieved for a non-specific target of CFTR. However, there is no evidence that the trans-splicing method would be operable in vivo.

Several articles published years after the filing date of the instant application point to the conclusion that trans-splicing in vivo is still far from being established as a reliable method of gene therapy. In an article published in July of 2001, Kikumori et al. (Hum. Gene Ther., vol. 12, pp. 1429-1441, 2001) provide evidence of the lack of specificity of trans-splicing. They teach that

attempts to replace mutant RET protooncogene sequence in NIH 3T3 cells and TT cells, using a PTM comprising a targeting domain and RET exon 16 (page 1430, paragraphs 4-7; Fig. 1; page 1432, paragraphs 5 and 6). One of the results was that PTM targeted to endogeneously expressed RET gene in TT cells failed to produce a specific trans-spliced product, but instead produced a variety of non-specific products (page 1436, second and third paragraphs). They concluded that even in NIH 3T3 cells with artificial RET constructs the efficiency of trans-splicing was low (page 1437, first paragraph) and there was a significant level of non-specific trans-splicing in the cells (page 1437, last paragraph; page 1440, first paragraph). Kikumori et al. end the paper with this statement:

"However, the ability of our PTMs to randomly trans splice with other cellular RNAs does raise some concerns regarding the safety of using this approach in gene therapy. For example, the potential for the creation or disruption of mRNA involved in normal cell function becomes limitless. This is certainly an issue that merits additional study to determine the extent and biological effects on nonspecific trans splicing for a variety of transduced RNA transcripts and explore possible mechanisms of reducing the level of nontargeted trans splicing." (page 1440, last paragraph).

Pergolizzi et al. recently reviewed trans splicing as a form of gene therapy (C.R. Biologies, vol. 327, pp. 695-709, 2004). They teach that targeting domain must be optimized on a case by case, trial and error basis (page 700, last paragraph; page 701, first paragraph), and that the efficiency and specificity of the trans splicing need to be improved (page 705, last paragraph; page 706).

Finally, Yang et al. (Mol. Ther., vol. 12, pp. 1006-1012, 2005) reviewed trans-splicing as a possible gene therapy modality. In the abstract the make the following statement:

"Recently published accounts that in vivo phenotypic correction of a variety of inherited diseases can be achieved by RNA repair are encouraging. Nevertheless, the science of RNA repair for treatment of human diseases is just beginning and faces several scientific and technical challenges that must be addressed and surmounted."

Again, as the other two cited references, Yang et al. stress that the issues of efficiency and specificity need to be addressed before the technique of trans splicing becomes acceptable for gene therapy (page 1010, third paragraph). They focus on the fact that there are a lot of factors which influence the efficiency of trans splicing, such as the target pre-RNA expression level, strength of the target splice sites, accessibility of the binding domain, strength of the PTM splice sites, and the route of PTM delivery (page 1010, fourth paragraph). Even though efficiencies of 70-80% are apparently achievable based on RT-PCR detection of spliced products, Yang et al. caution that RT-PCR detection does not correctly reflect the dynamics of RNA within the cell and dilution caused by RNA from heterogeneous cell populations (page 1010, fourth paragraph), and therefore they propose that a different assay should be used to assess the efficiency of splicing.

As to the specificity, Yang et al. state (page 1011, second paragraph):

"In the three components of RNA trans-splicing, there are few things we can do to control cellular spliceosome and target pre-mRNA for in vivo RNA repairing or reprogramming. Consequently, we should focus on the PTM, the only component that changes the overall dynamics between cis-splicing and trans-splicing inside cells."

They go on to state that basic information about how to manipulate the PTM is still missing, such as what is the best targeting intron, how to determine the length and sequence of the binding domain, how does the branch point sequence affect the process and what is the optimal distance

between the polypyrimidine tract and the 3' splice site. The authors conclude with this statement (page 1012):

"Twenty years ago RNA trans-splicing was first observed [35, 36] and recent progress in the past 5 years indicates pre-mRNA trans-splicing has advanced to the pre-clinical arena. Despite relatively low levels of trans-splicing, a significant impact on the phenotype has been demonstrated in animal models. Clearly the future of this field will require more efficient trans-splicing with the ultimate goal of using this technology for autosomal dominant disorders. This will be achieved with a greater understanding of trans-splicing regulation and the development of more sophisticated PTMs."

Therefore, ten years after filing date of Applicants' case, therapeutic trans splicing is still an area which is just being developed, thus, claims 54-60 lack enablement for in vivo applications.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to in vivo methods, including, for example, the best targeting intron for each gene, the length and sequence of the binding domain, the influence of branch point sequence on the process and the optimal distance between the polypyrimidine tract and the 3' splice site. Further, the effectivness of trans splicing depends on the type of vector used and the length of the sequence to be trans spliced to the endogeneous pre-mRNA. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the trans splicing of PTMs in vivo depend upon numerous known and unknown parameters, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the PTMs for in vivo treatment as broadly claimed (i.e encompassing a method in any cell under any treatment in any conditions). Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Interpretation

11. The claims 1-3, 16-18 and 50 are interpreted as any nucleic acid which comprises two nucleic acid segments (a targeting domain and the domain to be trans-spliced), since the limitations of "targeting domain" and "sequence to be trans-spliced" are intended use limitations which do not affect the structure of the nucleic acid. The preamble phrase "a modified synthetic nucleic acid molecule, wherein the modification enhances stability of the nucleic acid molecule" is not taken into account when comparing the claims to the prior art. First, from the structural point of view, the nucleic acid is the same whether it was obtained from the cell or synthesized. Further, there is no structural limitation in the claims which indicates that the nucleic acid has a structural modification which enhances its stability. Finally, the limitation "wherein the nucleic acid molecule is recognized by nuclear splicing components within the cell" is a matter of operating the invention,

which, again, does not result in a structural feature of the claimed nucleic acid molecule. The rejections presented below are based on two different interpretations of the claims.

12. The term "spacer region" has not been defined by Applicants, therefore it is interpreted as any number of nucleotides separating the 3' splice site from the other nucleic acid sequences.

13. The limitations of claims 7, 8, 22, 23, 42 and 43 refer to the intended use of the nucleic acid molecule, therefore they do not constitute structural limitations for the nucleic acid molecule itself.

14. The limitations of claims 13-15 and 28-30 "wherein the nucleic acid contains a nonsense mutation" is interpreted as the nucleic acid containing any of the three sequences TGA (or UGA), TAG (or UAG) or TAA (or UAA).

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1-5, 7, 8, 10, 11, 16-20, 22, 23, 25, 26, 36-40, 42, 43, 45, 46 and 48-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Reed (Genes and Development, vol. 3, pp. 2113-2123, 1989).

Claims 1-5, 7, 8, 10, 11, and 16-20, 22, 23, 25, 26 will be considered together, as they are identical.

Regarding claims 1, 7, 8, 16, 22 and 23, Reed teaches a nucleic acid molecule comprising two nucleic acid sequences, for example, exons 1 (= targeting domain) and exon 2 (= sequence to be trans-spliced) of a β-globin gene, a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site (Fig. 1; page 2122, third paragraph).

Regarding claims 2 and 17, Reed teaches a nucleic acid molecule comprising two nucleic acid sequences, for example, exons 1 and 2 of a β-globin gene, and a 3' splice acceptor site (Fig. 1; page 2122, third paragraph).

Regarding claims 3 and 18, Reed teaches a nucleic acid molecule comprising two nucleic acid sequences, for example, exons 1 and 2 of a β-globin gene, and a 5' splice site (Fig. 1; page 2122, third paragraph).

Regarding claims 4 and 19, Reed teaches a 5' donor site (Fig. 1).

Regarding claims 5 and 20, Reed teaches a number of nucleotides separating the 3' splice site from exon 1 (Fig. 1), therefore they teach a spacer separating the 3' splice site from the target binding domain.

Regarding claims 10, 11, 25 and 26, Reed teaches exon 2 of β-globin gene, which encodes a translatable polypeptide (Fig. 1).

Regarding claims 36, 42 and 43, Reed teaches a vector comprising an RNA polymerase SP6 promoter and a nucleic acid molecule comprising two nucleic acid sequences, for example, exons 1 (= targeting domain) and exon 2 (= sequence to be trans-spliced) of a β-globin gene, a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site (Fig. 1; page 2122, second and third paragraph).

Regarding claim 37, Reed teaches a vector comprising an RNA polymerase SP6 promoter and a nucleic acid molecule comprising two nucleic acid sequences, for example, exons 1 and 2 of a β-globin gene, and a 3' splice acceptor site (Fig. 1; page 2122, second and third paragraph).

Regarding claim 38, Reed teaches a vector comprising an RNA polymerase SP6 promoter and a nucleic acid molecule comprising two nucleic acid sequences, for example, exons 1 and 2 of a β-globin gene, and a 5' splice site (Fig. 1; page 2122, second and third paragraph).

Regarding claim 39, Reed teaches a 5' donor site (Fig. 1).

Regarding claim 5 and 40, Reed teaches a number of nucleotides separating the 3' splice site from exon 1 (Fig. 1), therefore they teach a spacer separating the 3' splice site from the target binding domain.

Regarding claims 45 and 46, Reed teaches exon 2 of β-globin gene, which encodes a translatable polypeptide (Fig. 1).

Regarding claims 48 and 49, Reed teaches synthesizing the nucleic acid molecules chemically, i.e. from oligonucleotides and in vitro (page 2122, second and third paragraph).

Regarding claim 50, Reed teaches a vector comprising an RNA polymerase SP6 promoter and a nucleic acid molecule comprising two nucleic acid sequences, for example, exons 1 (= targeting domain) and exon 2 (= sequence to be trans-spliced) of a β-globin gene, a 5' donor site, a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site (Fig. 1; page 2122, second and third paragraph).

Regarding claim 51, Reed teaches a number of nucleotides separating the 3' splice site from exon 1 (Fig. 1), therefore they teach a spacer separating the 3' splice site from the target binding domain.

17. Claims 2, 3, 5, 7, 8, 10, 11, 17, 18, 20, 22, 23, 25, 26, 31, 32, 50 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakashima et al. (Gene, vol. 141, pp. 193-200, 1994).

Claims 2, 3, 5, 7, 8, 10, 11 and 17, 18, 20, 22, 23, 25, 26 will be considered together, as they are identical.

Regarding claims 2, 7, 8, 17, 22 and 23, Nakashima et al. teach a YAC Y-1 molecule comprising a gene (= a nucleic acid molecule) comprising two nucleic acid sequences, for example,

exons 1 (= targeting domain) and exon 2 (= sequence to be trans-spliced) of a CCG1 gene and a 3' splice acceptor site (Fig. 1; page 195, paragraphs 1-3; Table 1).

Regarding claims 3 and 18, Nakashima et al. teach a YAC Y-1 molecule comprising a gene (= a nucleic acid molecule) comprising two nucleic acid sequences, for example, exons 1 (= targeting domain) and exon 2 (= sequence to be trans-spliced) of a CCG1 gene and a 5' splice site (Fig. 1; page 195, paragraphs 1-3; Table 1).

Regarding claims 5 and 20, Nakashima et al. teach a number of nucleotides separating the 3' splice site from exon 1 (Fig. 1; Table 1), therefore they teach a spacer separating the 3' splice site from the target binding domain.

Regarding claims 10, 11, 25 and 26, Nakashima et al. teach teaches exons 2 of CCG1 gene, which encodes a translatable polypeptide (Fig. 1).

Regarding claim 31, Nakashima et al. teach a nuclear localization signal (Fig. 1; Table 2).

Regarding claims 32, Nakashima et al. teach a YAC molecule (page 195, paragraphs 1-3), therefore they inherently teach a circular molecule.

Regarding claim 50, Nakashima et al. teach a YAC Y-1 molecule comprising a gene (= a nucleic acid molecule) comprising two nucleic acid sequences, for example, exons 1 (= targeting domain) and exon 2 (= sequence to be trans-spliced) of a CCG1 gene, a 3' donor site and a 3' splice site (Fig. 1; page 195, paragraphs 1-3; Table 1).

Regarding claim 51, Nakashima et al. teach a number of nucleotides separating the 3' splice site from exon 1 (Fig. 1; Table 1), therefore they teach a spacer separating the 3' splice site from the target binding domain.

18. Claims 2, 3, 13, 14, 17, 18, 28, 29 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by O'Prey et al. (Gene, vol. 84, pp. 493-499, 1989).

Regarding claims 2, 3, 17 and 18, O'Prey et al. teach genomic DNA of the rabbit 15-lipoxygenease comprising 13 introns and 14 exons, therefore comprising at least two nucleic acid sequences, 3' splice acceptor sites and 5' splice sites (page 494, second paragraph; page 495, second paragraph; Table I; Fig. 1).

Regarding claims 13, 14, 28 and 29, O'Prey et al. teach nonsense codons (Fig. 1, nucleotides 26-28, 43-45, 281-283, etc.).

Regarding claim 33, O'Prey et al. teach enhancers within introns 4 and 7 (Fig. 3).

19. Claims 2, 3, 17, 18, 34 and 53 are rejected under 35 U.S.C. 102(e) as being anticipated by Ares, Jr. et al. (U.S. Patent No. 5,773,244 A).

Regarding claims 2, 3, 17 and 18, Ares et al. teach a nucleic acid molecule construct comprising 3' half intron (= target binding domain), two exons and a 5' half intron (sequence to be trans spliced), together with the 3' and 5' splice sites (Fig. 1B; col. 2, lines 54-61).

Regarding claims 34 and 53, Ares et al. teach liposomes comprising the plasmid containing the construct (col. 7, lines 55-67; col. 8, lines 1-16).

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1-6, 16-21, 49, 50 and 54-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 3, 5, 7, 8, 10, 12, 13, 15-17, 19, 20, 22, 24, 25, 27, 29, 30, 32-34, 36, 37, 39, 41-44, 46, 47 and 49-78 of copending Application No. 10/103,294. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims of the 10/103,294 application are species of the instant claims.

Specifically, claim 1 of the instant application is drawn to a synthetic nucleic acid molecule comprising:

a) one or more target binding domains that target binding of the nucleic acid molecule to a pre-mRNA expressed within the cell;

b) a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site; and

c) a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell.

Claims 2 and 19 of the 10/103,294 application are drawn to a cell comprising a synthetic nucleic acid molecule containing, in addition to the elements of the molecule of claim 1, an intronic splicing activator and repressor binding site, and claim 36 of the 10/103,294 application is drawn to a nucleic acid molecule containing, in addition to the elements of the molecule of claim 1, an intronic splicing activator and repressor binding site, therefore anticipating claim 1. Claims 3 and 20 of the 10/103,294 application are drawn to a cell comprising a synthetic nucleic acid molecule containing, in addition to the elements of the molecule of claim 1, an insert of at least one mini intron sequence in the sequence to be trans spliced, and claim 37 of the 10/103,294 application is drawn to a nucleic acid molecule containing, in addition to the elements of the molecule of claim 1,

an insert of at least one mini intron sequence in the sequence to be trans spliced, therefore anticipating claim 1. Finally, claims 5 and 22 of the 10/103,294 application are drawn to a cell comprising a synthetic nucleic acid molecule containing, in addition to the elements of the molecule of claim 1, a ribozyme sequence, and claim 39 of the 10/103,294 application is drawn to a nucleic acid molecule containing, in addition to the elements of the molecule of claim 1, a ribozyme sequence, therefore anticipating claim 1. Since claim 16 of the instant application is identical to claim 1, these claims of the 10/103,294 application also anticipate claim 16.

Similarly, claims 2 and 17 of the instant application are anticipated by claims 7, 8, 10, 24, 25, 27 and 41-44 of the 10/103,294 application, and claims 3 and 18 are anticipated by claims 12, 13, 15, 17, 29, 30, 32, 34, 46, 47, 49 and 51 of the 10/103,294 application. The method claims 49 and 54 are anticipated by claims 52-66, 68 and 71 of the 10/103,294 application. Finally, the dependent claim 4 is anticipated by claims 69 and 70 of the 10/103,294 application, claim 5 by claims 15, 33 and 50 of the 10/103,294 application, claims 6, 21 and 52 of the instant application are anticipated by claims 72-75 of the 10/103,294 application, and claim 57 is anticipated by claims 76-78 of the 10/103,294 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claims 1-6, 16-21, 49 and 54-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-42 and 45-54 of copending Application No. 10/374,784. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims of the 10/374,784 application are species of the instant claims.

Specifically, claim 1 of the instant application is drawn to a synthetic nucleic acid molecule

comprising:

a) one or more target binding domains that target binding of the nucleic acid molecule to a pre-mRNA expressed within the cell;

b) a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site; and

c) a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell.

Claim 1 of the 10/374,784 application is drawn to a cell comprising a synthetic nucleic acid molecule containing, in addition to the elements of the molecule of claim 1, a spacer region that separates the 3' splice region from the target binding domain and a nucleotide sequence which encodes a reporter molecule to be trans spliced to pre-mRNA within a cell, and claim 27 of the 10/374,784 application is drawn to a nucleic acid molecule containing, in addition to the elements of the molecule of claim 1, a spacer region that separates the 3' splice region from the target binding domain and a nucleotide sequence which encodes a reporter molecule to be trans spliced to pre-mRNA within a cell, therefore anticipating claim 1. Claims 6-13 and 32-39 of the 10/374,784 application depend from claims 1 and 27, respectively, therefore they also anticipate claim 1 of the instant application. Since claim 16 of the instant application is identical to claim 1, these claims of the 10/374,784 application also anticipate claim 16.

Similarly, claims 2 and 17 of the instant application are anticipated by claims 2, 6-13, 28 and 32-39 of the 10/374,784 application, and claims 3 and 18 are anticipated by claims 3, 6-13, 29 and 32-39 of the 10/374,784 application. Dependent claims 4 and 19 are anticipated by claims 4, 6-13, 30 and 32-39 of the 10/374,784 application, claims 5 and 20 are anticipated by claims 1-4, 6-13 and

27-39 of the 10/374,784 application, and claims 6 and 21 are anticipated by claims 5-13 and 31-39 the 10/374,784 application.

Finally, the independent method claims 49 and 54 are anticipated by claims 14-16, 19-26, 40-42 and 47-54 of the 10/374,784 application, the dependent claim 55 is anticipated by claims 17-26, 45 and 47-54 of the 10/374,784 application, and the dependent claim 56 is anticipated by claims 18-26, 45 and 46 of the 10/374,784 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. Claims 1-3, 6, 16-18 and 21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 3, 5, 6, 9, 11, 26, 27, 29-32, 47, 48, 50, 52-55, 87 and 88 of copending Application No. 10/434,727. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims of the 10/374,784 application are species of the instant claims.

Specifically, claim 1 of the instant application is drawn to a synthetic nucleic acid molecule comprising:

a) one or more target binding domains that target binding of the nucleic acid molecule to a pre-mRNA expressed within the cell;

b) a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site; and

c) a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell.

Claim 5 of the 10/434,727 application is drawn to an adenovirus encoding a PTM containing, in addition to elements of the nucleic acid molecule of claim 1, a spacer region that

separates the 3' splice region from the target binding domain and the nucleotide sequence to be trans spliced encoding an adenovirus polypeptide required for adenovirus replication, therefore anticipating claim 1. Claim 29 of the 10/434,727 application is drawn to an adenovirus comprising a PTM, which, in addition to the molecule of claim 1, contains a spacer region that separates the 3' splice region from the target binding domain and the nucleotide sequence to be trans spliced encoding an adenovirus polypeptide required for adenovirus replication, and where the pre-mRNA is expressed by a pathogenic organism within a cell or induced in the cell infected by a pathogenic organism, therefore anticipating claim 1. Finally, claim 50 of the 10/434,727 application is drawn to an adenovirus comprising a PTM, which, in addition to the molecule of claim 1, contains a spacer region that separates the 3' splice region from the target binding domain and the nucleotide sequence to be trans spliced encoding an adenovirus polypeptide required for adenovirus replication, and where the pre-mRNA is expressed within a disease-associated cell, therefore anticipating claim 1. Since claim 16 of the instant application is identical to claim 1, these claims of the 10/434,727 application also anticipate claim 16.

Similarly, claims 2 and 17 of the instant application are anticipated by claims 2, 26 and 47 of the 10/434,727 application and their dependent claims 9, 11, 30, 32, 53-55, 87 and 88, and claims 3 and 18 of the instant application are anticipated by claims 3, 27 and 48 of the 10/434,727 application and their dependent claims 9, 11, 30, 32, 53-55, 87 and 88. Finally, the dependent claim 6 of the instant application is anticipated by claims 6, 31 and 52 of the 10/434,727 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. No references were found teaching or suggesting claims 6, 9, 12, 15, 21, 27, 30, 41, 44, 47, 52 and 54-60. Claims 6, 21 and 54-60 are rejected for reasons given above. Claims 9, 12, 15, 27,

30, 41, 44, 47, and 52 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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